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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,298	07/02/2001	Steven M. Ruben	PZ035P1C1	4425

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/895,298	RUBEN ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003 and 20 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-37,40-44,47-51,54-58 and 61-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-37,40-44,47-51,54-58 and 61-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 20, 2004 has been entered.

Status of Claims

2. Claims 25-37, 40-44, 47-51, 54-58 and 61-74 are pending in the instant application. Claims 37, 40, 44, 47, 51, 54, 58 and 61 have been amended and claims 38-39,45-46, 52-53 and claims 59-60 have been canceled as requested by Applicant in the Paper filed August 15, 2003. All claims are currently under examination.

Withdrawn Rejections

3. The rejection of claims under 112 § 1 for written description is withdrawn in view of Applicants' amendment filed August 15, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-37, 40-44, 47-51, 54-58 and 61-74 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record in the previous Office Action, Paper No. 7, at pages 4-6, Paper No. 9, at pages 7, the Paper Mailed November 20, 2003, and below.

Applicants traverse the rejection and submit on page 2 of the response that the Examiner failed to make a *prima facie* case for an enablement rejection. Applicants cite M.P.E.P. § 2164, and assert that the specification discloses a method of determining abnormal levels of a polypeptide in a biological sample, such that the enablement for use as a cancer marker is enabled. Applicants also submit that the standard for enablement is whether the experimentation needed to practice the invention is undue or unreasonable, and assert that establishing statistical certainty and/or disclosing sample numbers are not a requirement for patentability (M.P.E.P. § 2107.03).

Applicants' arguments have been fully considered but are not deemed persuasive. It is not disputed that the specification teaches how to determine polypeptide levels in biological samples, the issue is whether or not the polypeptide actually is overexpressed in cancer tissues and would be useful as a cancer marker. Although M.P.E.P. 2107.03 addresses utility, it is also relevant to enablement. M.P.E.P. 2107.03, Section I, states:

"As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty,

nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980)."

Although statistical certainty is not required, a reasonable correlation is required. The instant application has not provided a reasonable correlation between over-expression of the gene and use as a cancer marker.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988). It is acknowledged that the level of skill in the art is high, and it would not require undue experimentation for one of ordinary skill in the art to use the invention ***if*** it was demonstrated that there was a reasonable correlation between over-expression of the protein and cancer, which was based on a reasonable number of samples. However, given the state of the art, which shows the variability of expression of even established cancer markers in cancer tissues, it is not predictable from the assertion that the gene is primarily expressed in ovarian cancer and to a lesser extent in breast cancer and prostate tissue, that the protein could be used as a cancer marker, absent any disclosure of how many normal and cancer tissues were analyzed and the extent of expression. All the Wands factors are considered and it

is the balance of factors that determines whether a disclosure enables the use of the invention. In the previous Office Action, all of these factors were considered.

Applicants on pages 2-3 assert that they believe that the Examiner is questioning the credibility of the claimed invention as a cancer marker rather than its enablement as a cancer marker. However, as discussed in Office Action Paper No. 9, which Applicants cite on page 3, the credibility of the use of the polypeptide as a cancer was not doubted.

Applicants arguments on page 3 of the response that the specification as filed would enable one of ordinary skill in the art to practice the invention without undue experimentation, have been fully considered but are not deemed persuasive. The pages in the specification pointed to by Applicants describe general methods of determining levels of protein expression in biological samples, and the specification is enabling for measuring protein expression. However, the issue at hand is whether the specification is enabling for using the protein as a cancer diagnostic, which requires a reasonable correlation between difference in protein expression between cancer and normal tissue, which has not been sufficiently demonstrated.

On page 3 of the response, Applicants assert that that use of specific proteins as potential markers was well known in the art prior to the effective filing date of the instant application, and provide Anisowicz et al. as support. It is not disputed that specific proteins could be identified as potential cancer markers before the effective filing date of the instant application. An analysis of the Anisowicz et al. paper shows that a fairly large number of cell lines were analyzed for expression of the proposed cancer marker, protease M (page 625). On page 630, Figure 5A, Northern blots from normal and tumor lines of mammary tissue were analyzed for protease M mRNA expression. Three normal cell lines expressed the transcript at low levels, while ten

tumor cell lines did not have detectable message. Two primary cell lines as well as one metastatic cell line from the same patient had about 20-100 fold higher expression than normal cells, but the most metatastic cell line from the same patient expressed low levels. On page 631, Figure 6, a series of normal immortalized and primary tumor derived ovarian cell lines were examined for expression of protease M mRNA. The message was not expressed in any of the five normal immortalized cell lines, but was detected in five of the eight primary tumor cell lines examined. RNA was also examined from a series of normal ovarian tissue and biopsies from primary tumors, and while mRNA was not expressed in the three normal tissues examined, the six borderline ovarian tumor tissues, or the two metastatic tumors from colon primaries, it was expressed in 16 of the 20 primary ovarian tumor tissue specimens examined. From these results, the authors concluded that high protease M mRNA might serve as a marker for a subset of primary tumors. Anisowicz et al. is evidence that although there was some variability in expression, for example, expression of the mRNA in 16 out of 20 primary ovarian tumors, there is a good correlation between over-expression of this gene and cancer, and although the number of cells or tissues examined was not very large, a reasonable number of samples should be analyzed before the conclusion can be reached that a particular gene would be a potential cancer marker.

Applicants' arguments on pages 3-4 of the response that the Examiner appears to doubt the objective truth of the Applicants' disclosure, that the references Ferrari et al. and Clark et al., conclude that the markers tested can be used as cancer diagnostics even with variability of expression, and that even if expression is highly variable for a cancer marker, this does not prevent its use as a cancer marker, and the Maida et al. paper, which shows that elevated levels

of alpha-fetoprotein were demonstrated in a single patient to be indicative of cancer (Maida et al.), have been fully considered but are not deemed persuasive. The Examiner does not dispute that even though a particular marker may have variable expression, it could still be a useful cancer marker. However, the Ferrari et al. and Clark et al., references, as well as Anisowicz et al., demonstrate that a minimal number of samples must be analyzed to determine if there is some reasonable correlation between gene expression and use as a cancer marker. The central issue in the instant situation is that there was no disclosure of how many samples were analyzed or what the degree of the expression was. The objective truth of the expression information is not in doubt. However, based on the state of the prior art that demonstrates variability of expression of cancer markers and lack of information in the instant specification as to how many samples were analyzed and what the expression levels were, one of ordinary skill in the art would not conclude that the gene or encoded protein of the instant invention could be used as a cancer marker, based on the information provided in the specification.

Additionally, even if the specification enabled the use of the nucleic acids as cancer marker, the protein would not necessarily be useful as a cancer marker. Haynes et al. (Electrophoresis 19 :1862-1871, 1998) and Gygi et al. (Molecular and Cellular Biology, March 1999, p.1720-1730), studied 80 and 106 proteins, respectively, that were relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances, which varied by more than 50-fold. Haynes and Gygi concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Haynes, page 1863, 2nd paragraph, and Figure 1, Gygi, page 1727, Fig. 5). Anisowicz et al., provided by Applicants, is

further support that mRNA levels for the proposed cancer marker protease M are not always correlated with the protein levels. Anisowicz et al. showed that the primary tumor cell lines have 20 to 100 times more mRNA than normal cell strains, but the protein detected on Western blots was equal to or somewhat lower in the primary tumor cell lines than in the normal cell strains (page 632, Table 1).

On page 4 of the response Applicants note "determining enablement is a question of law based on underlying factual findings." M.P.E.P. § 2164.01, and reiterate that nowhere in either the M.P.E.P. of U.S. Code Title 35 does it state that statistical analysis/certainty is required for enablement of even patentability. As discussed above, statistical certainty or analysis not necessarily required; however, a reasonable correlation between expression of the gene and presence in cancer calls is required.

Therefore, due to the art which teaches gene expression in cancer cells can be variable even for cancer markers, that there is no strong correlation between level of mRNA expression and protein expression, and the lack of information in the specification regarding how many samples were assayed and level of expression, undue experimentation would be required to use the claimed invention.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

Official papers Before Final and After Final filed by RightFax should be directed to (703) 872-9306.

The customer service RightFax number is (703) 872-9305.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Eileen B. O'Hara, Ph.D.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Patent Examiner